REMARKS

Applicant respectfully requests reconsideration. Claims 26-48 were previously pending in this application. Claim 38 has been amended. Therefore claims 26-48 are pending for examination with claims 26 and 38 being independent claims. No new matter has been added.

Rejections under 35 U.S.C. §112

Claims 26-48 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. According to the Examiner the claims have been amended to recite "not antisense" as a limitation. Applicant respectfully disagrees.

Initially Applicant points out that claims 26 and 38 as filed included the limitation "not antisense". The term was not introduced through an amendment of these claims.

The Examiner states that the term "not antisense" as recited in the claims is not supported in the specification as filed. Applicants' arguments have been dismissed because according to the Examiner they relate to function of the molecules not structure. As stated in the prior response, the instant specification describes oligonucleotide analogs having "both therapeutic efficacy (through antisense or other means) and immunopotentiating activity." As the specification gives a number of alternatives for the activity of phosphorothioate oligonucleotide analogs, including immunopotentiating activity and antisense, the specification as filed therefore provides support for the term "not antisense". Antisense oligonucleotides function by binding to a complementary RNA sequence and preventing production of a protein. The function of antisense oligonucleotides is dictated by the structure. The primary structure of an antisense oligonucleotide, the nucleotide sequence, determines whether the oligonucleotide is complementary to an RNA. The reason for determining that the claim element is new matter based on a distinction between the function and structure of antisense is unclear to Applicant. The fact that applicant has taught in the specification that the oligonucleotides can work independent of an antisense method, clarifies that the invention is not limited to antisense oligonucleotides. Not all phosphorothioate containing oligonucleotides are antisense oligonucleotides.

Therefore, withdrawal of the new matter rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 26-48 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking in written description.

The Examiner states that the specification must provide sufficient distinguishing identifying characteristics such as "structure, physical or chemical properties, functional characteristics, and structure/function correlation." The Examiner states that not all oligonucleotides elicit an immune response, and cites McIntyre et al. (Antisense Research and development 3: 309-322, 1993) in support of this. The Examiner further states that Applicant has only offered Examples encompassing three sequences and that as such the genus is not enabled. Applicant disagrees.

The instant specification describes oligonucleotide analogs with at least one phosphorothioate bond in the backbone. It was found by the inventors that these phosphorothioate oligonucleotides can induce stimulation of an immune response in a sequence non-specific manner. Thus, the Applicant has described structure (an oligonucleotide with at least one phosphorothioate bond) and structure/function correlation (an oligonucleotide with at least one phosphorothioate bond induces an immune response). The MPEP states that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." MPEP § 2163.II.A.3.a.ii. (8th ed., rev. 2 2001). The standard for written description is whether the applicant had possession of the invention at the time the application was filed. In this case applicant described a class of molecules, oligonucleotides having at least one phosphorothioate bond for stimulating an immune response. Applicant had possession of the invention.

Accordingly, withdrawal of the rejection of claims 26-31, 33-37, and 39-48 under 35 U.S.C. §112 is respectfully requested.

Claims 26-48 were rejected under 35 U.S.C. §112 as allegedly lacking enablement. The Examiner acknowledges that the specification is "enabling for a method of stimulating a local immune response in a human by administering one phosphorothioate oligonucleotide analog, ISIS 2105" but maintains the previous statement that it "does not reasonably provide enablement for a method of stimulating a humoral immune response in a human using any phosphorothioate

oligonucleotide analogs in a patient with any type of cancer, any type of infection, and in combination with any type of surgery." Without conceding the Examiner's position, Applicant points out that the previously presented claims are not drawn to a humoral immune response, and therefore it is not necessary to enable stimulation of a humoral immune response. In the previous amendment Applicant amended claim 38 to specify a cell mediated immune response. At that time Applicant mistakenly neglected to amend the preamble to the claim. In this response Applicant has amended the preamble to claim 38 to specify a cell-mediated immune response.

The Examiner has stated that he was unable to find support for the argument that the specification discloses "the 'unexpected finding' that Applicants are now arguing which is that the phosphorothioate oligonucleotides stimulate an immune response in a sequence independent manner." Applicant directs the Examiner's attention to the specification on page 8 lines 10-27 or paragraph 16 and 17 of the published specification. It is taught that "it has now been found, surprisingly, that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. The immunostimulation does not appear to be related to any antisense effect which these oligonucleotide analogs may or may not possess."

One aspect of the present invention is based on the finding that oligonucleotides having at least one phosphorothioate linkage in their backbone can stimulate immune responses in a sequence independent manner. A common element of all the pending claims is the recitation of a phosphorothioate oligonucleotide analog that functions as an immunopotentiator. As defined in the specification, a phosphorothioate oligonucleotide analog is an oligonucleotide having at least one of its phosphodiester bonds replaced with a phosphorothioate linkage. According to the specification, the immunopotentiating effect is independent of the sequences of the oligonucleotide analogs used herein.

The Examiner maintained the rejection in view of the teachings of Allison et al. (Molecular Immunology 28: 279-284, 1991) to support his conclusion that the scope of the claims is not enabled because the "data provided in the specification is not commensurate in scope with the claims, which are drawn to methods of stimulating an immune response using any phosphorothioate oligonucleotide analogs." The Examiner has dismissed Applicant's prior arguments and asserted that the specification only teaches the use of *one* oligonucleotide, ISIS 2105. Applicant disagrees.

The specification describes the use of a class of molecules. The specific Examples in the specification describe data using ISIS 2105. However, working examples are not required. As such, the Applicant refers the Examiner to MPEP 2164.02 which states "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation" and that "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement". Applicant is not required to provide a working example for each and every species in order to enable the genus.

The Examiner cites Ratajczak et al. (PNAS USA 89:11823-11827, 1992) as teaching that the "administration of sequence specific sense, antisense, and control phosphorothioate oligonucleotides to mice result in different responses depending on the sequence administered" (page 11825, third full paragraph, lines 16-27). The Examiner cites Ratajczak et al to support his assertion that the "induction of splenomegaly and stimulation of B-lymphocyte proliferation in mice injected with phosphorothioate oligos occurs unpredictably in a manner that is dependent on the nucleotide sequence of the phosphorothioate oligonucleotide analogs". Applicant respectfully disagrees. Evaluation of splenomegaly and stimulation of B lymphocyte proliferation is one way of measuring a humoral immune response. A cell-mediated immune response may be evaluated, for instance, by measuring production of inflammatory cytokines such as IL-2, IFNγ, and TNFβ. Applicant has demonstrated efficacy of a phosphorothioate oligonucleotide analog in both antibody production and cytokine production. As stated previously, in the interest of furthering prosecution Applicant limited the claims to cell-mediated immune responses. The efficacy of the phosphorothioate oligonucleotide analog in eliciting a cell-mediated immune response has been demonstrated in the Examples.

The Examiner has stated a broad conclusion that the unpredictability of the invention was known or widely accepted in the art at the time the instant application was filed. The references supporting this assertion are provided to show that non-antisense oligonucleotides do not produce a particular response. However, if the prior art had shown a stimulation of cell mediated immunity that was due to the backbone modification as opposed to an antisense effect the invention would not

be novel. Applicant's discovery related to the phosphorothioate backbone modification and stimulation of cell mediated immunity is an important component of the invention.

The Examiner previously cited Vollmer et al. (Antisense and Nucleic Acid Drug Development 12:165-175, 2002) for the teaching that "non-CpG T-rich ODNs are always less efficient and potent than CpG ODNs", and that the mechanism of action by non-CpG "remains to be elucidated". Understanding mechanism is not a prerequisite to patentability. Applicant again points out that the results of Vollmer et al. are dosage-specific and that there is an optimal dose for activity of T-rich nucleic acid which may not be reflected in the data of Vollmer et al. In support thereof, the Examiner is directed to Figure 1 of Vollmer et al. which shows immunostimulation by a T-rich nucleic acid that is 17 nucleotides in length (ODN 5192). The dose-response data for this nucleic acid demonstrate that its stimulatory capacity increases substantially with increasing dose. The data highlighted by the Examiner in Figure 2 of Vollmer et al. corresponds to a single dose and there is no indication that it is necessarily the optimal dose for the nucleic acids tested. Additionally, the fact that phosphorothioate nucleotide analogs may be less immunostimulatory than CpG ODNs under some conditions is not relevant to patentability. Applicant need only show that the claimed method achieves its intended result, not that it achieves a better result than other methods. Applicant has met this burden by demonstrating that phosphorothioate nucleotide analogs are immunostimulatory. Applicant respectfully disagrees with the Examiner that Vollmer et al supports the Examiner's assertion of unpredictability.

Double Patenting Rejection

The Examiner rejected claims 26, 28, 29, and 30 as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 6,727,230 (Hutcherson et al.) in view of U.S. Patent 5,456,882 (Walker et al.).

Applicants may consider filing a Terminal Disclaimer if some claims are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

Accordingly, withdrawal of the rejection of claims 26, 28, 29, and 30 is respectfully requested.

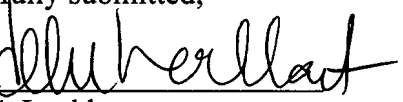
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check please charge any deficiency to Deposit Account No. 23/2825.

Dated: April 13, 2007

Respectfully submitted,

By 

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000